Docket No.: P0786.70002US005
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	John B. Sullivan *et al.*
Serial No.:	08/405,454
Confirmation No.:	6004
Filed:	March 15, 1995
For:	ANTIVENOM COMPOSITION CONTAINING FAB FRAGMENTS (As Amended)
Examiner:	Ronald B. Schwadron

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Dated: July 11, 2005

Michael T. Siekman, Reg. No. 36,276

REPLY BRIEF

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Appellants have submitted three Declarations providing separate and complementary facts supporting the three experts' unanimous conclusion that the prior art would not have rendered the claimed invention obvious. The Examiner's Answer vividly illustrates why the Examiner has not budged in the face of this evidence—the Examiner simply disagrees with the facts and conclusions contained in the Declarations. Because the Examiner has not provided any factual basis for disagreeing with those facts and conclusions, the rejections must be reversed.

I. The Evidence Shows That Fab Derived From An IgG Antivenom Would Not Have Been Expected To Be Effective

The Examiner's Answer repeatedly asserts that "there is no evidence" that one of ordinary skill in the art would have expected an Fab derived from an IgG antivenom not to be effective. [Answer at p. 12 ("no evidence of record that Fab"), p. 13 ("without providing any evidence"), p.15 ("no actual evidence of record").] The record, however, is replete with such evidence:

> **Because Fab is cleared rapidly**, one might have expected that a single administration of F(ab) antivenin would not effectively neutralize later-released antivenom. [Smith Decl. at ¶ 8.]
>
> **Because F(ab) fragments are relatively small (compared to intact immunoglobulins and $F(ab)_2$ fragments) and venom molecules are relatively large (compared to digoxin)**, one skilled in the art would have been concerned that a F(ab)-venom complex would retain toxicity. [Smith Decl. at ¶ 11.]
>
> Those of skill in the art did not expect F(ab) fragments to venom to be useful as antivenins. **The development of antivenin production through the years stopped at a final product of $F(ab)_2$'s.** For several reasons, it was not obvious that smaller fragments would be clinically efficacious . . . . **F(ab) is cleared more quickly than $F(ab)_2$, antivenin, or IgG. Slower clearance of large molecular weight venom proteins was know to be a fact.**
>
> * * *
>
> **The F(ab) with shorter T ½ and increased renal clearance, would <u>not be available</u> to bind venom.** Thus, one would reason, as did the experts at the time, that the use of F(ab) would be relatively or absolutely contraindicated **because toxicity might be prolonged and toxin, if redistributed, would be <u>more</u> harmful at other sites in the organism to which a short T ½ F(ab) would "taxi" and deposit the toxin, leaving it.** [Sullivan Decl. at ¶¶ 5,7.]
>
> [T]he failure of F(ab) antivenins was predicted **for the following reasons**:

- **F(ab) would cause redistribution of protein toxins to distant, nontargeted sites.**
- **F(ab) would act as a "taxi" and deposit venom poisons at various organs as it quickly left the body via the kidneys.**
- **F(ab)'s had failed with other drugs and protein poisons . . . in part because redistribution increased toxicity.** [Sullivan Decl. at ¶ 11.]

The shorter half-life of Fab fragments compared to the half-life of venom, and compared to the half-life of $F(ab)_2$ fragments, led researchers in the field to expect that antivenins comprising Fab fragments would not be effective against Crotalidae envenomation. [Russell Decl. at ¶ 32.]

Researchers in the field were **concerned that this rapid clearance and larger volume of distribution of Fab fragments compared to $F(ab)_2$ fragments would result in a more systematic toxicity than a localized one.** [Russell Decl. at ¶¶ 35, 36.]

[R]esearchers in the field were concerned that treatment with an antivenom comprising Fab fragments would be a harmful treatment for high molecular weight toxins, not an advisable treatment, **because the Fab fragments would redistribute high molecular weight toxins to areas of high blood flow, creating new toxicities and converting a localized toxicity into a systemic toxicity.** [Russell Decl. at ¶¶ 41, 44.]

As the bolded text shows, these numerous statements from the three Declarations are not just unsupported conclusions. They are supported by facts.

Indeed, the Smith Declaration contains six paragraphs of facts supporting its conclusions. [Smith Decl. at ¶¶ 6-11.] It explains that Fab fragments are cleared rapidly, while snake venom is released slowly from the site of a bite. [Smith Decl. at ¶ 8.] Those facts might have led one of ordinary skill in the art to expect that a single administration of an Fab antivenom would not effectively neutralize the later released antivenom. [Smith Decl. at ¶ 8.] Moreover, the large size of

venom proteins prevents a venom protein–Fab complex from being rapidly eliminated by the kidneys [Smith Decl. at ¶ 6], while the single binding site of an Fab fragment prevents a venom protein-Fab complex from being rapidly eliminated by the reticuloendothelial system. [Smith Decl. at ¶ 9.] Finally, the relatively small size of Fab fragments and the relatively large size of venom proteins would have led one skilled in the art to be concerned that the venom in an Fab-venom complex, which could not be rapidly eliminated by either the kidneys or the reticuloendothelial systems, would still retain its toxicity. [Smith at ¶ 10.]

The Sullivan Declaration contains eight paragraphs of facts supporting its conclusions. Like the Smith Declaration, it states Fab fragments are eliminated much more rapidly than venom proteins (24-26 hours versus weeks) and would not remain to bind venom. [Sullivan Decl. at ¶ 5.] The Sullivan Declaration also explains that the Fab fragments might also prolong the toxicity of venom proteins. [Smith Decl. at ¶ 5.] Again, the single binding site of Fab fragments would be expected to result in less repetitive binding to several venom proteins. [Sullivan Decl. at ¶¶ 6, 8]. Finally, the Sullivan Declaration explains that the rapid elimination of Fab fragments was expected to potentially redistribute and concentrate venom proteins in areas of high blood flow not normally affected by envenomation. [Sullivan Decl. at ¶¶ 5, 7.]

The Russell Declaration contains 13 paragraphs of facts supporting its conclusions. Fab fragments were expected to be less effective than $F(ab)_2$ fragments because they have only one antigen binding site. [Russell Decl. at ¶ 29.] Moreover, not only are venom proteins slowly eliminated due to their large size, but they are slowly released from the bite site. [Russell Decl. at ¶ 30.] Combined with the rapid elimination of Fab fragments due to their small size, researchers expected Fab fragments to soon not be available to bind venom proteins. [Russell Decl. at ¶ 32.]

Finally, the Russell Declaration explains that the larger volume of distribution of Fab fragments, combined with their rapid elimination, would result in redistributing venom toxins to high blood flow areas of the body, converting a localized toxicity to a systemic one. [Russell Decl. at ¶¶ 35-36.]

Thus, contrary to the Examiner's assertions, the Declarations do indeed provide actual evidence of nonobviousness.

II. The Examiner Has Provided No Evidence To Contradict The Facts And Resulting Conclusions In The Declarations

Rather than provide any evidence contradicting the facts and the resulting conclusions contained in the Declarations, the Examiner simply tries to dismiss them.[1]

A. The Declarations Do Not Depend Upon The Faulstich And Balthazar Articles

The Examiner repeatedly asserts that the Sullivan and Russell Declarations are based on a misinterpretation or distortion of the Faulstich and Balthazar publications. [Answer pp. 10, 11, 13.] This assertion does not even attempt to address the facts and conclusions of the Smith Declaration. And it does not actually address the facts and conclusions of the Sullivan Declaration because the Sullivan Declaration does not discuss either the Faulstich or the Balthazar articles.[2]

The Russell Declaration does discuss those two articles, but its facts and conclusions are most certainly not based upon any interpretation of them. Instead, the Russell Declaration provides 11 paragraphs of reasons why an Fab antivenom would not have been expected to work before even mentioning those articles. Then, the Russell Declaration states the concern that an Fab antivenom

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[1] Appellants are requesting an Oral Hearing because the arguments the Examiner makes in the Answer to dismiss the three Declarations have not been made before. Appellants did not request Oral Hearing in the Previous Appeal.

might redistribute and concentrate venom proteins in areas of high blood flow "was not merely a theoretical concern, as was later demonstrated by Faulstich et al." [Russell Decl. at ¶ 37.] It then discusses how the subsequent Balthazar article reinforced that concern. [Russell Decl. at ¶¶ 39-40.] Thus, the facts and conclusions of the Russell Declaration are not based upon those two articles. It is based upon the facts discussed in its paragraphs 26-36. As the Declaration states, the conclusion from those facts was merely confirmed and reinforced by those two articles; it did not depend upon them:

> [R]esearchers in the field were concerned that treatment with an antivenom comprising Fab fragments would be a harmful treatment . . . . Faulstich et al. confirmed this concern . . . . Balthazar et al. reinforced this concern . . . . [Russell Decl. at ¶¶ 41-42.]

B. The Declarations Do Not Contradict Appellants' Statements Concerning $F(ab)_2$ Antivenoms

The Examiner attempts to dismiss the Smith Declaration on the ground that it contains no teaching that an Fab_2 antivenom is less effective than an IgG antivenom and that it states that Fab_2 antivenoms have been used. [Answer at p. 9.] Similarly, the Examiner attempts to dismiss the statements in the Sullivan and Russell Declarations regarding an Fab_2 antivenom on the ground that the specification allegedly contradicts them by stating that they should be more effective than an IgG antivenom. [Answer at pp. 9, 13.] While the Examiner's statements are true, that in no way affects the evidentiary weight of the Declarations. The evidence shows that, despite the knowledge that the smaller the antibody fragment, the less chance of serum sickness, the art had not progressed past Fab_2 antivenom to Fab antivenom. [Sullivan Decl. at ¶ 5; Russell Decl. at ¶ 26.] The art

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[2] To the extent the Sullivan Declaration discusses digoxin and α-amatoxin, like the Russell Declaration, its conclusions do not depend upon results involving those two toxins. Rather, those results are just additional facts supporting its conclusions. [Sullivan Decl. at ¶ 11.]

stopped because they were concerned the single antigen binding site, high volume of distribution, and rapid elimination of Fab fragments compared to venom proteins would result in an Fab antivenom being, not just less effective than an Fab_2 antivenom, but actually harmful. [Sullivan Decl. at ¶ 7; Russell Decl. at ¶¶ 26, 43.]

III. The Examiner's Dismissal Of The Evidence In The Declarations Is Improper

As competent evidence tending to show the nonobviousness of the claimed invention, the three Declarations "must be accorded fair weight." *In re Piasecki,* 745 F.2d 1468, 1474 (Fed. Cir. 1984). The perfunctory dismissal of the Declarations reveals they were not accorded fair weight. As in *Piasecki,* it appears that each fact in the Declaration, "when it was evaluated at all, was evaluated against the [obviousness] conclusion itself rather than against the facts on which the conclusion was based. The *prima facie* case remained set in concrete." *Piasecki,* 745 F.2d at 1473.

The failure to evaluate the facts in the Declarations against the facts the Examiner relied upon is particularly improper in this case. Appellants have acknowledged that the concern of serum sickness had already led those skilled in the art to develop $F(ab)_2$ antivenoms, that the Coulter article teaches Fab fragments against a particular snake venom toxin, and that the Smith article teaches Fab fragments could be advantageous due to their more rapid and more extensive distribution. In such a case where the references appear to tend to render the claimed invention obvious, facts contained in Declarations "may often be the most probative and cogent evidence in the record." *Stratoflex, Inc.* v. *Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983). Such evidence "may often establish that an invention appearing to have been obvious in light of the prior art was not." *Id.*

Without knowledge of the rapid and extensive distribution of Fab fragments compared to venom proteins and the related potential to redistribute and concentrate venom proteins in areas of high blood flow, the claimed invention might appear obvious. With that knowledge, it does not.

Indeed, evaluating the facts supporting the rejection against the facts in the Declaration is quite revealing. The Answer quotes the Smith article three different times concerning the alleged motivation stemming from the advantages of Fab fragments. [Answer at pp. 7, 13, 15.] The quoted portions discuss the rapid distribution of Fab fragments, the extensive distribution of Fab fragments, and the rapid clearance of Fab fragments. These are the very facts the Declarations rely upon to show that the claimed invention would not have obvious.

After Appellants' invention, it might seem simple to progress from $F(ab)_2$ antivenom to Fab antivenom, but hindsight informed by Appellants' specification is not a basis for evaluating patentability. Such hindsight must be particularly avoided where the claimed invention appears, in retrospect, to be simple. *In re Oetiker*, 977 F2d 1443, 1447 (Fed. Cir. 1992).

IV. The Answer Makes Several False Accusations Regarding The Appeal Brief

A. Related Appeals and Interferences

The Examiner alleges that the Appeal Brief "failed to disclose" that the §103 rejection of previously pending claims 45-47 was affirmed in the Previous Appeal. [Examiner's Answer at p. 2.] But the Appeal Brief expressly disclosed that fact. [Appeal Brief at p. 4.] The Appeal Brief did not mention one rejection from the Previous Appeal, but the Board reversed that § 112 rejection.

B. Summary of the Invention

The Examiner alleges that, contrary to the Summary of the Invention, the Coulter article[3] taught that Fab was known to neutralize a large molecular weight toxin *in vivo.* [Answer at p. 3.] As discussed at pages 13-14 of the Appeal Brief, the Coulter article did not teach that Fab fragments could be used *in vivo* to neutralize a large molecular weight toxin because the Fab fragments were first mixed with the toxin and then the Fab-toxin complex was injected intravenously. Results from such premixing cannot be extrapolated to predict *in vivo* results because neutralization by Fab fragments by such *in vitro* pre-mixing "does not reflect their *in vivo* efficiency." [Sorkine abstract[4].]

The Examiner also asserts that the Fab antivenom had "a far greater" antivenom activity than a commercially purified antivenom, not a whole antivenom *per se*. Appellants do not understand how this might affect the patentability of the claimed invention. Perhaps it is to provide context for the next statement that Table 3 shows that Fab fragments do not necessarily provide a higher degree of protection than IgG purified from commercial antivenom. [Answer at p. 3.] Table 3, however, indicates that both Fab fragments and IgG protected all 4 mice tested. [Specification at p. 20.] Thus, it does not show that IgG fragments are more protective than Fab fragments in certain situations. Rather, it shows a ceiling effect where all subjects were protected. Indeed, this Table

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[3] The Examiner asserts that the Stedman reference defines antivenin as "an antitoxin specific for an animal or insect toxin." [Answer at p. 6 (emphasis added).] But it actually defines antivenin as "an antitoxin specific for an animal or insect venom." [Stedman's at p. 94.] Moreover, Appellants defined an antivenom as "a suspension of venom neutralizing antibodies prepared from the serum of animals . . . hyperimmunized against a specific venom or venoms." [Specification at p. 4, lines 19-22.] As the Russell Declaration explains in detail, venoms comprise numerous individual toxins. [Russell Decl. at ¶¶ 15-19.] The Coulter article involved a single toxin of a snake venom, not the entire snake venom, so that its antiserum was an antitoxin, not an antivenom. [Russell Decl. at ¶ 46-47.]

[4] The Examiner asserts that the Sorkine abstract discloses that Fab successfully neutralized toxin whether they were premixed or not [Answer at p. 12] and that premixing results reflect actual *in vivo* results. [Answer a p. 13.] Regardless of the Examiner's interpretation of Sorkine's results, the fact remains that that Sorkine state that premixing results, such as Coulter's, do not reflect the expected *in vivo* efficiency: "the *in vitro* neutralization of the venom by immunoglobulin fragments does not reflect their *in vivo* efficiency." [Sorkine.] The Sorkine abstract is not available as prior art.

shows that the 4-hour Fab digest was equally effective as the 48-hour Fab digest, even though the 4-hour Fab digest was not complete. [Specification at p. 17, line 28-31.]

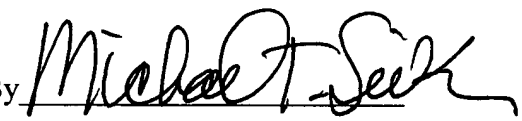
Finally, the Examiner dismisses Appellants' arguments regarding CroFab on the ground that it is an ovine preparation. [Answer at p. 8.] Of course, the claims are not limited to a particular antibody source. Moreover, the Smith article concerns an ovine preparation. [Smith article at p. 384.] Data from an ovine preparation cannot be relevant to dispute patentability but irrelevant to support it.

V. Conclusion

The Examiner refused to weigh the facts contained in the Declarations against the facts supporting the rejections. That refusal was factually wrong; the Examiner's attacks on the Declarations are simply incorrect. That refusal was also legally wrong; the Examiner should have considered the facts rebutting the rejections and weighed them against the facts supporting the rejections, not against the rejections itself. Such an analysis would have revealed that many of the very facts the Examiner relies upon, when put into context, actually show that the claimed invention was not obvious. The rejections should be reversed.

Dated: July 11, 2005

Respectfully submitted,

By 

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